Viral Hemorrhagic Fevers

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Viral Hemorrhagic Fevers

- Fever, myalgia, headache, prostration
- Hemorrhage
- Capillary leak
- Hypotension, shock, death

Hemorrhagic Fever

An acute febrile illness characterized by malaise, myalgia, and prostration dominated by generalized abnormalities of vascular permeability, and regulation. Bleeding manifestations often occur, particularly in severe cases; they are usually diffuse and reflect widespread vascular damage rather than life-threatening volume loss.

Hemorrhagic Fever Viruses: Taxonomy

- Four families of lipid-enveloped viruses with single-stranded RNA genomes
  - Arenaviruses
  - Bunyaviruses
  - Filoviruses
  - Flaviviruses

Hemorrhagic Fever Virus Families

Arenaviridae

- New World Complex
  - Argentine HF — Junin Virus
  - Bolivian HF — Machupo Virus
  - Venezuelan HF — Guanarito Virus
  - Brazilian HF — Sabia Virus
- Old World Complex
  - Lassa Fever — Lassa Virus

Hemorrhagic Fever Virus Families

Bunyaviridae

- Phlebovirus Genus
  - Rift Valley Fever — RVF Virus
- Nairovirus Genus
  - Crimean-Congo HF — CCHF Virus
- Hantavirus Genus
  - HFRS
    - Korean or Epidemic HF — Hantaan
    - E. Europe — Dobrava-Belgrade
    - Nephropathia Epidemica — Puumula Virus
    - Rat-borne — Seoul

Hemorrhagic Fever Virus Families

Filoviridae

- Ebola HF — Ebola Virus
- Marburg HF — Marburg Virus

Flaviviridae

- **Mosquito-Borne:**
  - Yellow Fever — YF Virus
  - Dengue HF — Dengue Viruses
- **Tick-Borne:**
  - Kyasanur Forest Disease — KFD Virus
  - Omsk HF — OHF Virus

Hemorrhagic Fever Viruses: Ecology

- **Maintained in animal reservoirs**
  - **Arenaviruses: Rodents**
  - **Bunyaviruses:**
    - **CCHF: Hares, birds, ticks**
    - **Rift Valley: Mosquitoes**
    - **Hantaviruses: Rodents**
  - **Filoviruses: Unknown**
  - **Flaviviruses**
    - **Dengue:Monkeys, humans, mosquitos**
    - **Yellow fever: Monkeys, mosquitoes**

Transmission to Humans

- **Aerosols**
  - **Desiccated rodent excreta: Arenaviruses, hantaviruses**
  - **Generated by field mice caught in agricultural machinery: New World arenaviruses**
  - **Generated during slaughter of infected livestock: CCHF, RVF**
- **Contaminated food/water**
  - **Arenavirus (Lassa)**

Transmission to Humans

- **Arthropod vectors:**
  - Mosquitoes
    - **Bunyavirus: RVF**
    - **Flaviviruses: Dengue, Yellow fever**
  - Ticks
    - **Bunyavirus: CCHF**
    - **Flaviviruses: Kyanasur Forest Disease, Omsk HF**
  - Hematophagous flies:
    - **Bunyaviruses: RVF**

Transmission to Humans: BW Implications

- **With exception of dengue, all VHF agents transmitted by aerosol in laboratory (animal models)**
- **Stabilization in aerosols**

Are Viral Hemorrhagic Fevers Important Health Problems?

- **Global interest in VHFs:Most of world population at risk**
- **Argentine HF** — **100-1000's of cases disruptive to agriculture**
- **Lassa fever** — **up to 20% of febrile admissions in some W. Africa hospitals**
- **Rift Valley fever** — **broad distribution in Africa; epidemics in 1977,1993-4, 1998**
- **Congo-Crimean HF** — **broad geographic distribution epidemics and nosocomial outbreaks**

Are Viral Hemorrhagic Fevers Important Health Problems? *(cont.)*

- **HFRS**
  - Annual epidemics in Asia and elsewhere
  - Broad geographic distribution
  - Up to 200,000 cases annually, with half occurring in China
  - Cases among US troops in Korea and Bosnia
  - Seoul virus infects urban rats in USA
  - 3 cases HFRS due to Seoul virus identified in Baltimore

◊ Glass et al. J Infect Dis 1993;167:614-20
◊ Glass et al. Nephron 1994;68:48-51

Are Viral Hemorrhagic Fevers Important Health Problems? *(cont.)*

- **Dengue HF**
  - Endemic in Asia, Indonesia
  - Epidemics in Central America and Caribbean due to expanding range of *Aedes aegypti*
  - Domestically acquired cases- Texas, Florida
  - Over 1 million cases and 100,000 deaths annually due to dengue HF
- **Yellow fever**
  - Annual sylvatic epidemics
  - Potential for urban epidemics
  - High mortality rate among unvaccinated
  - Limited vaccine production potential world-wide

Military Relevance: Endemic/Epidemic VHF

- **International Deployments**
- **Risk of Importation/Exportation of Disease**
- **Impact on Training and Mobilization**
- **Impact on Medical Readiness**

Military Relevance: Biological Warfare Threats

- **Pro:**
  - Highly infectious by aerosol
    - **Stabilizers to enhance viability**
  - High morbidity/mortality
  - Replicate well in cell culture
- **Con:**
  - Lack of vaccine/Rx to protect user

Viral Pathogenesis

- **Complex, incompletely understood, varies with specific viruses**
- **Activation of complement/cytokine cascades**
- **Activation of coagulation cascades**
- **Role of organ system failures**
  - **Yellow Fever: Hepatic failure, deficiency of Vitamin K dependent clotting factors**
  - **HFRS: Uremia, platelet dysfunction**
- **Key event: Damage to vascular endothelium**

Typical VHF Patient

- **History**
  - Foreign travel to endemic or epidemic area
  - Rural environs (except dengue, urban YF)
  - Nosocomial exposure
  - Contact with arthropod or rodent reservoir
  - Domestic animal blood exposure (CCHF, RVF)
- **Incubation**
  - Typical 5-10 days
  - Range 2-16 days **(except Hantavirus: 9-35 days)**

Typical VHF Patient

- Symptoms
  - Fever, headache, malaise, dizziness
  - Myalgias
  - Nausea/vomiting
- Initial Signs
  - Flushing, conjunctival injection
  - Periorbital edema
  - Petechiae
  - Positive tourniquet test
  - Hypotension

VHF Evolution

- Prostration
- Pharyngeal, chest or abdominal pain
- Mucous membrane bleeding, ecchymosis
- Shock
- Usually improving or moribund within a week (except HFRS, arenaviruses)
- Bleeding, CNS involvement, marked elevation SGOT portend poor prognosis
- Mortality agent dependent (<10-90%)

VHF Sequelae

- Prolonged Convalescence
- Hair Loss, Furrowed Nails
- Deafness (Lassa, EBO)
- Retinitis (RVF, KFD)
- Uveitis (RVF, MBG)
- Encephalitis (AHF, BHF, RVF, KFD, OHF)
- Pericarditis (Lassa)
- Renal insufficiency (HFRS)

VHF Clinical Lab

- Leukopenia is suggestive, but WBC may be normal, elevated, or leukemoid
- Thrombocytopenia is typical, but sometimes mild or absent
- Hematocrit normal or increased early
- AST (SGOT) typically elevated; prognostic value
- BUN/Cr related to circulatory status (except in HFRS)

VHF Clinical Lab *(cont.)*

- Bilirubin, amylase may be elevated
- Prothrombin/APTT usually prolonged
- FSP normal or modestly elevated
- Fibrinogen elevated, normal, or decreased
- Proteinuria usual

VHF: Differential Diagnosis

- Bacterial
  - typhoid fever, meningoccemia, rickettsioses, leptospirosis
- Protozoal
  - falciparum malaria
- Other
  - vasculitis, TTP, HUS, heat stroke

Diagnosis of Zoonotic Viruses

- **Epidemiology critical**
- **Clinical impressions valuable but often ambiguous**
- **Exclude life-threatening items in DDX:**
  - Bacterial sepsis:blood cultures
  - Malaria: thick and thin blood smears (Giemsa stain)
- **Laboratory Confirmation:**
- **Rapid ELISA techniques most easily employed**
  - **viral antigen detection sensitive to ~10^4 log PFU/ml**
  - **IgM antibody capture**
- **Serology on paired sera may be definitive or highly suggestive**

Laboratory Confirmation (Cont'd)

- **Nucleic acid hybridization & immunohistochemistry (IHC) of formalin-fixed tissues; Electron microscopy**
  - **can provide definitive evidence**
- **Virus isolation from acute blood or necropsy best**
- **Polymerase chain reaction (PCR)**
  - **increasingly important tool; undergoing further development**

Processing Clinical Specimens

- **isolation of virus (Biosafety Level 4)**
  - **whole blood (w/ anticoagulant)**
  - **urine, throat swab or wash**
    - **in sealed plastic tube w/10% FBS or 1%HSA final conc.**
  - **label each specimen swab exterior of each container with disinfectant**
  - **double-bag, swab exterior with disinfectant *before* removal from patient's room**

VHF Management: Cardiovascular

- **Hemodynamic resuscitation & monitoring**
  - invasive (S-G catheter) as warranted and feasible
- **Careful fluid management**
  - **use of colloid**
  - **hemodialysis or hemofiltration as needed**
    - **esp. HFRS patients**
- **Vasopressors and cardiotonic drugs**
- **Cautious sedation and analgesia**

VHF Management Hematologic

- **DIC may be important in some VHFs (RVF, CCHF, Filoviruses)**
- **Coagulation studies and clinical judgement as guide**
  - replacement of clotting factors
  - platelet transfusions
- **No antiplatelet drugs or IM injections**

VHF Management Anti-viral Therapy

- **Ribavirin**
  - *Arenaviridae* (Lassa, AHF, BHF)
  - *Bunyaviridae* (HFRS, RVF, CCHF)
- **Immune (convalescent) plasma**
  - *Arenaviridae* (AHF, BHF, ?Lassa)
  - Passive immunoprophylaxis post-exposure?

Lassa Fever & CCHF Management Ribavirin

- **Treatment**
  - 30 mg/kg IV single loading dose
  - 16 mg/kg IV q 6 hr for 4 days
  - 8 mg/kg IV q 8hr for 6 days
- **Prophylaxis**
  - 500 mg PO q 6 hr for 7 days

Note: Parenteral and oral ribavirin are investigational and available through human use protocols only

McCormick JB *et. al. N Eng J Med* 314(1):20-26, 1986.
Jahrling PB *et al. J Infect Dis* 141:580-589, 1980.

HFRS Therapy Ribavirin

- **fever of ≤ 6 days**
- **intravenous ribavirin treatment regimen:**
  - **33 mg/kg (2.0 gm/60kg) single loading dose**
  - **16 mg/kg (1.0 gm/60kg) q 6h for 4 days**
  - **8 mg/kg (0.5 gm/60kg) q 8h for 3 days**

Huggins et. al. *J Infect Dis* 164:1119-27, 1991.
Note: parenteral ribavirin is investigational and available through human use protocol only

VHF Management Other

- **R/O or treat empirically for malaria, typhoid fever, rickettsioses, *etc.***
- **vigilance against secondary bacterial infections**
  - nosocomial pneumonia, UTI, bacteremia

ONLY INTENSIVE CARE WILL SALVAGE THE SICKEST PATIENTS

Infection Control (Arenavirus, Filovirus, CCHF)

- **Single room w/ adjoining anteroom as only entrance**
  - **Handwashing facility with decontamination solution**
    - **0.5% sodium hypochlorite, 2% glutaraldehyde, phenolic detergent, soap**
    - **Changing area/protective equipment**
- **Negative air pressure; air not recirculated**
  - **Prominent hemorrhage, cough, vomiting, diarrhea**
  - **Consider negative air flow room, if available, in absense of these sxs/sxs to avoid having to transfer pt later**

CDC. Update: Management of patients with suspected viral hemorrhagic fever. *MMWR* 44 (No. 25):475--479, June 30, 1995.
CDC. Management of patients with suspected viral hemorrhagic fever. *MMWR* 37 (No. S-3):1-15, February 26, 1988.

Infection Control (Arenavirus, Filovirus, CCHF) (Cont'd)

- **Strict barrier precautions**
  - **gloves, gown, mask, shoe covers, protective eyewear/faceshield**
- **HEPA-filtered mask or respirator**
  - **Prominent hemorrhage, cough, vomiting, diarrhea**

CDC. Update: Management of patients with suspected viral hemorrhagic fever. *MMWR* 44 (No. 25):475--479, June 30, 1995.
CDC. Management of patients with suspected viral hemorrhagic fever. *MMWR* 37 (No. S-3):1-15, February 26, 1988.

Infection Control Arenavirus, Filovirus, CCHF (cont.)

- **Chemical toilet**
- **All body fluids disinfected**
- **Disposable equipment & sharps into rigid containers containing disinfectant -> autoclaved or incinerated**
- **Double-bag refuse**
  - outside bag disinfected then autoclaved or incinerated

CDC. Update: Management of patients with suspected viral hemorrhagic fever. *MMWR* 44 (No. 25):475--479, June 30, 1995.
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VHF Management
Protection of Medical Personnel

- **Patient care limited to minimal # of caregivers**
  - *reliable* and *competent-minimize exposure risk*
- **Education**
  - barrier nursing practices, exercise of due care
  - consult AIT, USAMRIID

DO NOT PANIC

High Level Containment
Disadvantages

- **systems hinder patient care**
- ***increase* possibility of parenteral exposure**
- **personnel must be trained to safely and effectively function**
- **require similar BL-4 laboratory support**
- **expensive**
- **1^{O} & 2^{O} medical care personnel must deal w/ suspected VHF patient before such specialized help is available**

Clinical Laboratory Procedures

- **Strict barrier precautions**
  - gloves, gown, mask, shoe covers, protective eye/faceshield
  - consider respirator with HEPA filter
  - handle specimens in biosafety cabinet when possible
- **Spills/splashes**
  - immediately cover with disinfectant, allow to soak for 30'
  - wipe with absorbent towel soaked in disinfectant
- **Waste disposal**
  - same as for patient isolation practices

CDC. Management of patients with suspected viral hemorrhagic fever. *MMWR* 37 (No. S-3):1-15, February 26, 1988.

Exposures
First Aid

- **Wash/irrigate wound/site *immediately***
  - within 5 minutes of exposure
- **Mucous membrane (eye, mouth, nose)**
  - continuous irrigation with rapidly flowing water or sterile saline for ≥ 15 minutes
- **Skin**
  - scrub for at least 15' minutes while copiously soaking the wound with soap or detergent solution
    - fresh Dakin's solution (0.5% hypochlorite): dilute 1 part standard laundry bleach (5% hypochlorite) with 9 parts tap water

Exposures: Surveillance

- **Casual contacts**
  - remote contact with index patient (*e.g.*, same airplane)
  - no known risk
- **Close contacts**
  - household, physical, nursing care, handling lab specimen
  - record temp b.i.d. for 3 weeks post-exposure
  - post-exposure prophylaxis measures warranted if develop fever (T≥101F) or other systemic symptoms within 3 weeks post-exposure

CDC. Management of patients with suspected viral hemorrhagic fever. *MMWR* 37 (No. S-3):1-15, February 26, 1988.

Post-Exposure Prophylaxis

- **High-risk contacts**
  - mucous membrane (*e.g.*, kissing, sexual intercourse); needlestick or other penetrating injury involving exposure to patient's secretions, excretions, blood, tissues, or other body fluids
  - post-exposure prophylaxis measures warranted if available

VHF Vaccines

- **YELLOW FEVER**
  - licensed 17D vaccine safe and efficacious
  - cannot be used in persons with egg allergy
- **ARGENTINE HEMORRHAGIC FEVER**
  - live, attenuated
  - safe and efficacious; used in 150,000
  - protects monkeys against Bolivian HF

VHF Vaccines

- **RIFT VALLEY FEVER**
  - formalin-inactivated
    - safe but requires 3 shots, intermittent booster
    - limited supply
  - live, attenuated MP-12
    - Phase II testing
- HFRS (HANTAAN)
  - vaccinia vectored recombinant vaccine

Aeromedical Isolation Team

- **High-level protection against small-particle aerosol infection**
  - Plastic isolator for transport stretcher
    - negative pressure with HEPA exhaust
  - Positive pressure suits for medical personnel
- **Medical consultation**
  - contact USAMRIID and ask for MOD on call
    - DSN 343-2257, (301) 619-2257
  - Transport arrangements
    - Maj Nerges: DSN 343-4647; sky pager (800) 901-6233
    - can transport 1-2 patients

Viral Hemorrhagic Fevers

Disease	Geography	Source of Human Infection[a]	Incubation (days)
Lassa	Africa	Rodent (Nosocomial)	5-16
AHF/BHF	South America	Rodent	7-14
RVF	Africa	Mosquito (Slaughter)	2-5
CCHF	Europe, Asia, Africa	Tick (Slaughter of domestic animal)	3-12
HFRS	possibly world-wide	Rodent	9-35
Marburg/Ebola	Africa	Unknown (Nosocomial)	3-16
Yellow Fever	Tropical Africa, South America	Mosquito	3-15
Dengue HF	Asia, Americas, Africa	Mosquito	3-15
KFD/OMSK	Mysore, India/ Russia	Tick (Muskrat-contaminated water)	3-8

[a]Usual source in nature (other routes in parentheses).

Viral Hemorrhagic Fevers

Taxon	Disease	Clinical	Pathogenesis
Arenaviridae	Lassa fever	Hemorrhage & neurologic involvement seen in severe cases; deafness; pericarditis may occur during recovery	High AST and viremia predict fatal outcome
	Argentine & Bolivian HF	Prominent neurologic manifestations; petechiae and hemorrhage common	Bone marrow and CNS infection
Bunyaviridae			
Phlebovirus	Rift Valley fever	retinitis; hemorrhage and hepatitis with icterus occur infrequently	DIC in monkey model
Nairovirus	Crimean-Congo HF	copious hemorrhage & extensive ecchymoses may dominate clinical picture more prominently than with other HF	
Hantavirus	Hemorrhagic fever with renal syndrome	Renal involvement prominent intrinsic disease feature; long incubation period	Tubular lesion. Onset of disease correlates with immune response

Viral Hemorrhagic Fever

Disease	Maintenance	Amplification	Infection of man	Human to Human
Lassa	Rodent: *Mastomys natalensis*		Aerosol, fomites	Contact Nosocomial (occasional)
Argentine HF	Rodent: *Calomys musculinus*	Other rodents?	Aerosol, fomites	Venereal (occasional) Nosocomial (rare)
Bolivian HF	Rodent: *Calomys callosus*		Aerosol, fomites	Venereal (suspected) Nosocomial (rare)
Rift Valley fever	Mosquito: flood water *Aedes*	Sheep & cattle with other mosquitoes	Mosquito bite (biological transmission, interrupted feeding)	needlestick
			Aerosol or fomites from slaughter of domestic animals	

Viral Hemorrhagic Fever *(cont.)*

Disease	Maintenance	Amplification	Infection of man	Human to Human
Congo-Crimean HF	Ticks: principally *Hyalomma*	Intermediate tick hosts	Tick bite. Crushing tick; slaughter or milking of infected animal. Fomite or aerosol	Nosocomial (occasional) (occasional)
HFRS	Rodents: several genera of Muroidae superfamily		Aerosol, possibly fomites	None
Marburg	Unknown		Unknown	Contact
Ebola				Nosocomial
Yellow fever				
Sylvan	Mosquito-primate cycle; *Aedes* in Africa and *Haemagogus* in Americas principally Transovarial in mosquitoes and ticks rarely	Primates	Mosquito bite	needlestick

Viral Hemorrhagic Fevers *(cont.)*

Taxon	Disease	Clinical	Pathogenesis
Filoviridae	Marburg disease, Ebola HF	Extreme prostration, cachexia, maculopapular rash, abdominal pain, diarrhea common; high (>50%) mortality	DIC implicated
Flaviviridae			
Mosquito	Yellow fever	Black vomit; jaundice with midzonal liver necrosis	B-cell necrosis; terminal hepatorenal syndrome?
	Dengue HF	Maculopapular rash, arthralgias, vascular permeability with petechiae, edema, and hemorrhage	Antibody enhancement of macrophage infection; complement activation
Tick	Kyasanur Forest disease, Omsk HF	Pulmonary involvement; biphasic illness with subsequent CNS disease	

Viruses	Disease	In vitro neutralization by convalescent sera	In vitro Interferon Sensitivity	Ribavirin
Arenaviridae	Lassa fever	+	low	yes
	Argentine & Bolivian HF	++	low	yes
Bunyaviridae				
Phlebovirus	Rift Valley fever	+++	yes	yes
Nairovirus	Congo-Crimean HF	+?	yes	yes
Hantavirus	HFRS, HPS	+++	yes	yes
Filoviridae	Marburg disease, Ebola HF	0	low	no
Flaviviridae				
Mosquito borne	Yellow fever	+++	yes	low
	Dengue HF	+++	yes	low
Tick borne	Kyasanur Forest disease, Omsk HF	+++	yes	low

Argentine, Bolivian, and Venezuelan Hemorrhagic Fevers

- **rodent-borne (aerosol) in South America**
  - nosocomial transmission rare
- **petechiae & other hemorrhages neurologic manifestations w/ normal CSF**
- **incubation period 7-14 days**
- **shock, pulmonary edema, GI hemorrhage, CNS dz (tremors, dysarthria, seizures)**
- **lab: low wbc, plt, and complement; proteinuria, prerenal**
- **Dx: Ag detection and IgM capture ELISA virus isolation (serum, buffy coat, semen)**

Lassa Fever

- **rodent-borne in West Africa**
  - nosocomial: exposure to body fluids
- **pharyngitis with exudate, hypotension, cough, abd pain, edema and effusions, lymphadenopathy**
  - hemorrhage not common except in severe cases
  - deafness, pericardial friction rub during recovery
- **incubation period 5-16 days**
- **elevated AST, CPK, and amylase; protenuria; mildly low or normal wbc and plt**
- **Dx: Ag detection and IgM capture ELISA virus isolation from serum, urine, throat**

Congo-Crimean Hemorrhagic Fever

- **tick-borne in Africa, Asia, E. Europe, Middle East**
  - nosocomial via body fluid exposure (?aerosol)
- **extensive hemorrhage and ecchymoses, hypotension, hepatomegaly, abdominal pain, jaundice, toxicity**
- **incubation period 3-12 days**
- ***Low* plt & fibrinogen, elevated PT/PTT & FSP, lymphopenia, elevated LFT's and bili**
- **Dx : Ag detection and IgM capture ELISA virus isolation (serum)**

Rift Valley Fever

- **mosquito-borne in sub-Saharan Africa**
  - nosocomial infection not reported but aerosol transmission possible
- **fever, headache, myalgias, retinitis**
  - infrequently complicated by hemorrhage, severe hepatitis with jaundice, and/or encephalitis
- **incubation period 2-5 days**
- **low wbc and plt, transaminitis with elevated bili and alk phos, prolonged PT/PTT**
- **Dx : Ag detection and IgM capture ELISA virus isolation (serum)**

Hemorrhagic Fever with Renal Syndrome

- **rodent-borne (aerosol)**
  - HFRS: Asia (Hantaan, Seoul), Europe (Hantaan, Dobrava), USA (Seoul)
  - nephropathia epidemica in Europe (Puumala)
  - May complicate HPS due to Bayou, Black Creek Canal, and South American hantaviruses
- **fever, shock, hemorrhage, renal failure**
- **incubation period 9-35 days**
- **low plt, renal azotemia**
- **Dx : IgM capture ELISA**

Ebola and Marburg

- **unknown reservoir in Central and East Africa**
  - nosocomial: transmission usu. via exposure to body fluids, but possible by fomite or droplet
- **severe prostration with delirium, maculopapular rash, DIC**
  - abdominal pain, petechiae, GI hemorrhage, hepatitis, edema, prerenal azotemia, shock
- **incubation period 3-16 days**
- **low wbc, plt; positive FSP; transaminitis; proteinuria, azotemia**
- **Dx: virus isolation from serum, urine, semen, throat or rectal swab**

Yellow Fever

- **mosquito-borne in tropical Americas and sub-Saharan Africa**
- **jaundice, midzonal liver necrosis, black vomit, relative bradycardia**
- **incubation period 3-15 days**
- **low wbc and plt, proteinuria, elevated SGOT, prolonged PT/PTT**
- **Dx : IgM capture ELISA virus isolation (serum)**

Dengue Hemorrhagic Fever

- **mosquito-borne in tropical Americas, Africa, Asia**
- **maculopapular rash sparing palms and soles, arthralgias, capillary friability**
  - positive tourniquet test, petechiae and mucosal hemorrhage, shock
- **incubation period 3-15 days**
- **low plt and fibrinogen, lymphocytosis, hemoconcentration, depressed C3 and C4**
- **Dx : IgM capture ELISA virus isolation (serum, buffy coat)**

Pathogenesis: Dengue Hemorrhagic Fever

- **Four different serotypes of Dengue virus**
- **Initial infection: Neutralizing Ab vs. intial strain**
- **Re-infection due to different serotype: Non-neutralizing Ab**
  - **Immune complexes c live virus**
  - **Enhanced uptake by monocytes**
  - **Infection/lysis of monocytes-release of cytokines, anticoagulants, procoagulants**
- **Implications re vaccine development**

Kyasanur Forest Disease
Omsk Hemorrhagic Fever

- **tick-borne in India (KFD) and Siberia (Omsk)**
  - nosocomial transmission not reported
- **systemic toxicity, pulmonary infiltrates biphasic course with later CNS involvement**
  - becomes afebrile, then develops neurologic disease
- **incubation period 3-8 days**
- **low wbc and plt**
- **Dx: IgM capture ELISA**